REMARKS/ARGUMENTS

Present Invention and Pending Claims

Claims 1-8 and 15-23 are pending. Claims 1-8 are directed to a pharmaceutical composition. Claims 15-23 are directed to a method of treating a cardiovascular disorder.

Summary of the Office Action

Claims 5-8 have been rejected under 35 U.S.C. § 112, second paragraph, as allegedly indefinite. Claims 1-8 have been rejected under 35 U.S.C. § 103(a), as allegedly obvious over Gumkowski et al. (U.S. Patent Application Publication 2003/0022944) in view of Ault et al. (U.S. Patent 7,049,283), Huang et al. (*Clinical Science*, 103: 587-594 (2002)), and Cayman Chemical Company ("JTT-705;" August 18, 2009). Claims 15-23 have been rejected under 35 U.S.C. § 103(a), as allegedly obvious over Gumkowski et al. in view of Ault et al., Huang et al., and Vascular Web (2009). Reconsideration of the pending claims is hereby requested.

Priority

As acknowledged by the Examiner, the pending application was filed March 17, 2004, and claims priority to four provisional applications:

- U.S. Provisional Patent Application 60/455,293 filed March 17, 2003;
- U.S. Provisional Patent Application 60/460,521 filed April 4, 2003;
- U.S. Provisional Patent Application 60/477,202 filed June 10, 2003; and
- U.S. Provisional Patent Application 60/493,649 filed August 8, 2003.

The Examiner notes on page 3 of the Office Action that the subject matter of claims 2-5 and 18-23 is not entitled to any of the priority dates. As such, according to the Examiner, "[c]laims 2-5 and 18-23 are given a priority date of October 4, 2006" (Office Action, page 3, second paragraph). It is unclear to Applicants how the Examiner ascertained the alleged effective filing date of October 4, 2006, for the indicated claims. Since the present application was filed on March 17, 2004, the effective filing date for any claim in the pending

application could not be after March 17, 2004. Applicants would appreciate clarification from the Examiner on this point.

Discussion of the Indefiniteness Rejection

Claims 5-8 allegedly are indefinite because the metes and bounds of the term "substantially" are unclear. According to the Office Action, the term "substantially" is "not defined by the claim, the specification does not provide a standard for ascertaining the requisite degree, and one of ordinary skill in the art would not reasonably be appraised of the scope of the invention" (Office Action, page 3, fourth paragraph).

Applicants traverse this rejection based on the following discussion.

Claim 5 is directed to a pharmaceutical composition comprising (i) a substantially crystalline cholesteryl ester transfer protein inhibitor, wherein the amount of inhibitor in amorphous form does not exceed about 10% and (ii) a water-insoluble concentration-enhancing additive, wherein the cholesteryl ester transfer protein inhibitor is JTT-705. The Examiner alleges that the claim does not recite the metes and bounds of the phrase "substantially crystalline." This contention is incorrect. Claim 5 clearly states, "wherein the amount of inhibitor in amorphous form does not exceed about 10%." The explicitly recited upper limit of "about 10%" amorphous material clearly establishes the metes and bounds of the amount of JTT-705 that is "substantially crystalline," i.e., about 90% or more.

Further, the Office Action states that the "the specification does not provide a standard for ascertaining the requisite degree." This contention also is incorrect. The specification at, for example, paragraph 0078, states: "The amount of crystalline CETP inhibitor can be measured by powder X-ray diffraction, Scanning Electron Microscope (SEM) analysis, differential scanning calorimetry (DSC), or any other standard quantitative measurement."

Based on the foregoing, it is clear that the claims establish the metes and bounds of the term "substantially crystalline" and that the specification describes how to ascertain the requisite degree. Therefore, Applicants maintain that one of ordinary skill in the art would reasonably understand the meaning and scope of this term, such that independent claim 5 (as

well as claims 6-8, which are dependent thereon) is not indefinite. Applicants respectfully request the withdrawal of the indefiniteness rejection.

Discussion of the Obviousness Rejection

A. Gumkowski et al., Ault et al., Huang et al., and "Cayman Chemical"

Claims 1-8 allegedly are obvious over Gumkowski et al. in view of Ault et al., Huang et al., and "Cayman Chemical." Gumkowski et al. discloses self-emulsifying pharmaceutical compositions that are liquid solutions, suspensions, and oil-in-water emulsions. The compositions comprise a CETP inhibitor (one of many examples of which is JTT-705), and other co-solvents, surfactants, and optionally a digestible oil. Ault et al. discloses a solid pharmaceutical composition for oral delivery comprising an active agent, crospovidone or povidone, and a delivery agent for the active agent. Ault et al. also discloses solid pharmaceutical compositions comprising calcitonin and either crospovidone or povidone. While Ault et al. does not disclose the use of JTT-705 as a CETP inhibitor, Huang et al. allegedly discloses that JTT-705 is a known CETP inhibitor. Cayman Chemical allegedly discloses that JTT-705 is a crystalline solid.

According to the Examiner, it would have been obvious to one of ordinary skill in the art to formulate a composition comprising a CETP inhibitor, such as JTT-705, and crospovidone because crospovidone is known to enhance bioavailability of pharmacological agents, as taught by Ault et al.

According to the Office Action, the reference referred to as "Cayman Chemical" has a publication date of "8/18/2009," i.e., August 18, 2009 (Office Action, page 4, third full paragraph). Applicants are unsure as to how the Examiner arrived at a publication date of August 18, 2009, for this reference. "Cayman Chemical" indicates (in the upper right hand corner of the first page) that it was revised on October 30, 2006, and printed the next day on October 31, 2006. This printed revised version differs from the reported earlier version revised on March 11, 2003, which in turn superseded the original created on August 18, 1999. Thus, "Cayman Chemical" has a publication date of October 31, 2006, not August 18, 2009 (as indicated in the Office Action) or August 18, 1999 (if that what was intended to be recited in the Office Action). "Cayman Chemical" does not reflect what information existed

in the original version created on August 18, 1999, or in the revised version created on March 11, 2003, and further does not reflect whether that original version or revised version were ever published, let alone at about those dates. Since a publication date of October 31, 2006, is well *after* the present application's filing date of March 17, 2004, "Cayman Chemical" is not prior art to the present invention, as defined by the pending claims, under any subsection of section 102.

The subject matter defined by claims 1-8 would not have been obvious to one of ordinary skill in the art based on the combination of Gumkowski et al., Ault et al., Huang et al., and "Cayman Chemical" even if "Cayman Chemical" were properly relied upon as prior art. It is even more clear that the obviousness rejection is improper in the absence of "Cayman Chemical" as a reference, as discussed in more detail below.

Out of the hundreds of disparate CETP inhibitors disclosed therein, Gumkowski et al. does not contain anything pointing one of ordinary skill in the art to JTT-705 (see paragraphs 0113-1035). As acknowledged by the Examiner, Gumkowski et al. does not teach or suggest a composition comprising crospovidone, as required by product claims 1-4 and 8 (and method claims 15-23). Gumkowski et al. also does not disclose the crystalline form of the CETP inhibitor, as required by product claims 2-8. In fact, Gumkowski et al. describes the opposite by stating that the self-emulsifying formulations contain "no visibly detectable crystallization of CETP inhibitor" (paragraphs 0036, 0037, and 1060).

As conceded by the Examiner, Ault et al. does not disclose JTT-705. Ault et al. also does not disclose the use of CETP inhibitors *at all* or even the treatment of cardiovascular disorders.

According to the Examiner, "[i]t would have been obvious to one of ordinary skill in the art to formulate a composition comprising a CETP inhibitor, such as JTT-705, and crospovidone because crospovidone is known to enhance the oral bioavailability of pharmacological agents as taught by Ault et al. and CETP inhibitors are known to have low oral bioavailability, per Gumkowski et al." (Office Action, page 5, fifth paragraph). This alleged reason set forth by the Examiner ignores the fact that Gumkowski et al. discloses *hundreds* of disparate CETP inhibitors – only one of which is JTT-705. One of ordinary skill in the art would not have been led to select JTT-705 based on Gumkowski et al. unless one of

ordinary skill in the art already had in mind JTT-705. Of course, starting with JTT-705 before even reading Gumkowski et al. could only involve hindsight knowledge of the present invention, which is impermissible, since the elements of a pending claim cannot be used as a blueprint for piecing together an obviousness rejection. "'The invention must be viewed not with the blueprint drawn by the inventor, but in the state of the art that existed at the time.... That which may be made clear and thus 'obvious' to a court, with the invention fully diagrammed and aided ...' by experts in the field, 'may have been a breakthrough of substantial dimension when first unveiled.'" *Uniroyal Inc. v. Rudkin-Wiley Corp.*, 837 F.2d 1044, 1050-1051, 5 U.S.P.Q.2d 1434, 1438 (Fed. Cir. 1988), quoting *Interconnect Planning Corp. v. Feil*, 774 F.2d 1132, 1138, 227 U.S.P.Q. 543, 547 (Fed. Cir. 1985).

The Examiner further fails to set forth a credible reason as to why one of ordinary skill in the art would turn to Ault et al. after considering the disclosure of Gumkowski et al. While the Examiner alleges that CETP inhibitors have low oral bioavailability and that Ault et al. discloses a method of increasing bioavailability of "pharmacological agents" (Office Action, page 5, fifth paragraph), Applicants note that Ault et al. discloses a solid pharmaceutical composition for oral delivery comprising an active agent (e.g., calcitonin), crospovidone or povidone, and a delivery agent for the active agent. Calcitonin is not a CETP inhibitor and is structurally diverse from JTT-705. Thus, the Examiner provides no credible reason for one of ordinary skill in the art to have consulted the disclosure of Ault et al. in the course of preparing a composition of Gumkowski et al., let alone that one of ordinary skill in the art would have reasonably expected the utilization of crospovidone in the composition of Gumkowski et al. to have a beneficial effect on that composition.

Thus, given the disparate teachings of Gumkowski et al. and Ault et al., one of ordinary skill in the art would have had no reason to even try using the crospovidone disclosed in Ault et al. in a CETP inhibitor-containing composition of Gumkowski et al. because Ault et al. is not directed to the use of *any* CETP inhibitors or the treatment of cardiovascular disorders.

Huang et al. discloses the use of JTT-705 to treat atherosclerosis. Huang et al. does not disclose the use of crystalline JTT-705 or the treatment of hyperlipidemia. Therefore,

Huang et al. does not provide (i) the necessary missing link between Gumkowski et al. and Ault et al. or (ii) the required crystallinity element of claims 2-8.

In view of the absence of any credible reason for one of ordinary skill in the art to select JTT-705 based on Gumkowski et al. and to combine the disclosures of Gumkowski et al. and Ault et al. with any reasonable expectation of success, and the further failure of Gumkowski et al., Ault et al., and Huang et al. to disclose JTT-705 that is substantially crystalline, such that the amorphous form does not exceed about 10%, the present invention must be considered to be unobvious over the combination of Gumkowski et al., Ault et al., and Huang et al. (since "Cayman Chemical" is unavailable as prior art). Accordingly, Applicants respectfully request that the obviousness rejection based on the combination of Gumkowski et al., Ault et al., Huang et al., and "Cayman Chemical" be withdrawn.

B. Gumkowski et al., Ault et al., Huang et al., and Vascular Web

Claims 15-23 allegedly are obvious over the combination of Gumkowski et al., Ault et al., Huang et al., and "Vascular Web." Gumkowski et al., Ault et al., and Huang et al. are discussed above in the context of the other obviousness rejection. "Vascular Web" allegedly discloses that the treatment of hyperlipidemia involved the lowering of low density lipoprotein (LDL) cholesterol.

The document referred to as "Vascular Web" by the Examiner is a print out from an internet website on December 16, 2009. No other date is provided in the disclosure of this reference. Thus, the publication date of the document appears to be December 16, 2009, which date is well *after* the present application's filing date of March 17, 2004. Thus, "Vascular Web" is not available as prior art to the pending application under any subsection of section 102.

The subject matter defined by claims 15-23 would not have been obvious to one of ordinary skill in the art based on the combination of Gumkowski et al., Ault et al., Huang et al., and "Vascular Web" even if "Vascular Web" were properly relied upon as prior art. In the absence of "Vascular Web" as a reference, it is even more clear that the obviousness rejection is improper. The combination of the remaining references, i.e., Gumkowski et al., Ault et al., and Huang et al., does not render the present invention as defined by claims 15-23

obvious for the same reasons that the combination of these same references does not render the present invention as defined by claims 1-8 obvious as discussed above inasmuch as claims 15-23 directly or indirectly depend on claim 1. Accordingly, Applicants respectfully request that the obviousness rejection based on the combination of Gumkowski et al., Ault et al., Huang et al., and "Vascular Web" be withdrawn.

Conclusion

Applicants respectfully submit that the patent application is in condition for allowance. If, in the opinion of the Examiner, a telephone conference would expedite the prosecution of the subject application, the Examiner is invited to call the undersigned.

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Date: April 5, 2010